Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight[1–3]

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ABSTRACT

Background: After weight loss, total energy expenditure—in particular, energy expenditure at low levels of physical activity—is lower than predicted by actual changes in body weight and composition. An important clinical issue is whether this reduction, which predisposes to weight regain, persists over time.

Objective: We aimed to determine whether this disproportionate reduction in energy expenditure persists in persons who have maintained a body-weight reduction of ≥10% for >1 y.

Design: Seven trios of sex- and weight-matched subjects were studied in an in-patient setting while receiving a weight-maintaining liquid formula diet of identical composition. Each trio consisted of a subject at usual weight ($Wt_{initial}$), a subject maintaining a weight reduction of ≥10% after recent (5–8 wk) completion of weight loss ($Wt_{loss\text{-}recent}$), and a subject who had maintained a documented reduction in body weight of >10% for >1 y ($Wt_{loss\text{-}sustained}$). Twenty-four-hour total energy expenditure (TEE) was assessed by precise titration of fed calories of a liquid formula diet necessary to maintain body weight. Resting energy expenditure (REE) and the thermic effect of feeding (TEF) were measured by indirect calorimetry. Nonresting energy expenditure (NREE) was calculated as NREE = TEE – (REE + TEF).

Results: TEE, NREE, and (to a lesser extent) REE were significantly lower in the $Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$ groups than in the $Wt_{initial}$ group. Differences from the $Wt_{initial}$ group in energy expenditure were qualitatively and quantitatively similar after recent and sustained weight loss.

Conclusion: Declines in energy expenditure favoring the regain of lost weight persist well beyond the period of dynamic weight loss. *Am J Clin Nutr* 2008;88:906–12.

INTRODUCTION

In lean and obese adults studied during or shortly (<3 mo) after weight loss, our group (1–6) and others (7–15) have shown significant reductions in energy expenditure (EE) beyond those predicted solely on the basis of changes in weight and body composition. Fewer investigators have examined the consequences of longer-term maintenance of reduced weight on measures of EE (16). Such studies are important to distinguish between possible "carryover" persistence of declines in EE characterizing the period of active weight loss and longer biological responses to decreased energy stores per se. Some authors have suggested that this reduction in EE persists for prolonged periods after weight loss (1, 12, 16–22), whereas others (23–27) have reported no changes in EE corrected for changes in body mass and composition at any point after weight reduction. The question of whether declines in EE after weight loss persist in the long term is critical to understanding the physiologic basis for the high rate of recidivism to obesity after otherwise successful weight reduction (28, 29).

The varied and conflicting results of studies of this question were reviewed in detail elsewhere (30, 31). A recent review published in this journal concluded that studies of weight-reduced obese subjects that used chamber calorimetry or the differential excretion rates of ^2H_2O and $H_2{}^{18}O$ did not conclusively show a significant reduction in EE after weight loss (30). A number of possible sources of error in studies attempting to address this critical question, including the absence of weight stability at the time of testing, an overly brief period of weight stability, and a lack of weight-matched controls, were discussed. Other possible confounders included variations in diet composition and levels of physical activity.

We have conducted studies of energy metabolism before and after weight reduction in obese and nonobese subjects whose physical activity is monitored, whose weight stability is clearly documented, and who ingest only a liquid formula diet for months at a time while living in a clinical research center (CRC). Using this design, we have been able to control for possible differences in diet composition, subject compliance, and physical activity and to stabilize weight to levels of constancy not possible in out-patient studies. We are also able to avoid assumptions regarding physical activity.

Within our subject population of >100 persons, 7 subjects have maintained a weight loss of ≥10% for ≥1 y before entry into this study, and those subjects are designated here as $Wt_{loss\text{-}sustained}$). We contrasted their EE with the EEs of sex- and weight-matched subjects who had been admitted to the study at usual body weight (designated here as $Wt_{initial}$) or who had been admitted to the study at usual body weight and then

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TABLE 1
Subject characteristics[1]

Trios and groups	Age	Race-ethnicity	Weight	Fat-free mass	Fat mass
	y		*kg*	*kg*	*kg*
Trio 1: women					
$Wt_{loss\text{-}sustained}$	41	White	67.1	45.9	21.2
$Wt_{initial}$	20	White	65.7	43.3	22.4
$Wt_{loss\text{-}recent}$	21	African American	67.1	42.9	24.2
Trio 2: women					
$Wt_{loss\text{-}sustained}$	36	White	67.6	44.2	23.4
$Wt_{initial}$	34	White	66.6	44.2	22.4
$Wt_{loss\text{-}recent}$	24	White	69.6	43.9	25.7
Trio 3: women					
$Wt_{loss\text{-}sustained}$	41	White	80.1	54.0	26.1
$Wt_{initial}$	27	White	79.2	46.3	32.9
$Wt_{loss\text{-}recent}$	21	African American	80.0	57.3	22.7
Trio 4: men					
$Wt_{loss\text{-}sustained}$	35	African American	78.3	70.1	8.2
$Wt_{initial}$	37	White	74.6	63.3	11.3
$Wt_{loss\text{-}recent}$	19	White	76.6	63.7	12.9
Trio 5: men					
$Wt_{loss\text{-}sustained}$	32	White	95.0	69.4	25.6
$Wt_{initial}$	28	African American	94.5	72.9	21.6
$Wt_{loss\text{-}recent}$	34	Pacific Islander	100.2	64.9	25.3
Trio 6: women					
$Wt_{loss\text{-}sustained}$	30	Hispanic American	146.0	64.4	81.6
$Wt_{initial}$	26	African American	142.8	62.4	80.4
$Wt_{loss\text{-}recent}$	33	African American	145.2	71.6	73.6
Trio 7: women					
$Wt_{loss\text{-}sustained}$	23	African American	163.6	81.0	82.6
$Wt_{initial}$	19	African American	157.0	83.1	74.6
$Wt_{loss\text{-}recent}$	40	White	149.1	65.3	83.8
Overall values					
$Wt_{loss\text{-}sustained}$	34.0 ± 2.4[2]		99.7 ± 14.8	61.1 ± 5.2	38.4 ± 11.5
$Wt_{initial}$	27.3 ± 2.5		97.3 ± 14.2	59.4 ± 5.8	37.9 ± 10.5
$W_{loss\text{-}recent}$	28.9 ± 2.9		98.3 ± 13.2	58.5 ± 4.2	38.3 ± 10.6

[1] $Wt_{loss\text{-}sustained}$, subjects maintaining a weight loss of ≥10% over periods ranging from 1 to 6 y and reporting being weight-stable for ≥1 y; $Wt_{initial}$, subjects at their usual weight who have been weight-stable for ≥6 mo; $Wt_{loss\text{-}recent}$, subjects who have lost ≥10% of their weight on an in-patient basis and have maintained the reduced weight for ≥3 wk. By design, there were no significant differences in weight between groups.

[2] $\bar{x}$ ± SEM (all such values).

reduced to ≤90% of their starting weight (designated as $Wt_{loss\text{-}recent}$).

SUBJECTS AND METHODS

Subjects

During the past 20 y, we have studied >100 subjects who participated in prolonged in-patient (ie, CRC) studies of weight maintenance at usual and altered body weight. These were lean and obese healthy subjects who had been weight-stable for ≥6 mo at their maximum lifetime weights and healthy subjects maintaining a stable weight that was ≥10% below their maximal lifetime weight for ≥1 y before admission. Most subjects were studied while maintaining their usual body weight and then again while maintaining their weight for ≈2 mo after a weight loss of ≥10% achieved as in-patients. Seven subjects (5 females and 2 males) maintaining a reduced body weight for periods ranging from 1 y to 6 y before enrollment ($Wt_{loss\text{-}sustained}$ subjects) were compared with 7 sex- and weight-matched subjects studied at their usual body weight ($Wt_{initial}$ subjects) and another 7 sex- and weight-matched subjects studied while maintaining a weight loss of ≥10% for 5–8 wk after in-patient weight reduction ($Wt_{loss\text{-}recent}$ subjects). Each subject match was made by selecting the $Wt_{initial}$ subject and the $Wt_{loss\text{-}recent}$ subject of the same sex whose weight was closest to that of a $Wt_{loss\text{-}sustained}$ subject. These trios (1 $Wt_{loss\text{-}sustained}$ subject, 1 $Wt_{initial}$ subject, and 1 $Wt_{loss\text{-}recent}$ subject) composed a total of 7 groups. No subject was included in more than one group. All $Wt_{loss\text{-}sustained}$ subjects were able to document with medical records that they had maintained a body-weight reduction of ≥10% for >1 y before enrollment. All $Wt_{initial}$ and $Wt_{loss\text{-}recent}$ subjects had been stable at their maximal lifetime weights for ≥6 mo before admission to the study. All subjects were in good health and were taking no medications. Subject characteristics are presented in **Table 1**.

Written informed consent was obtained from all subjects. Studies were approved by the institutional review boards of the Rockefeller University Hospital and The New York Presbyterian Medical Center, and the protocols were consistent with the principles guiding research involving humans (32).

Protocol

Subjects lived in a CRC throughout these studies and were fed only a liquid formula diet [40% of calories as fat (corn oil), 45% as carbohydrate (glucose polymer), and 15% as protein (casein hydrolysate)], plus vitamin and mineral supplements, in quantities sufficient to maintain a stable weight (defined as an average daily weight variation of <10 g/d for ≥2 wk) (6).

$Wt_{initial}$ subjects were studied after their weight had been stabilized as in-patients at their usual body weight. $Wt_{loss\text{-}recent}$ subjects were studied during weight stability after an in-patient weight reduction of ≥10% achieved by consuming 800 kcal/d of the liquid formula over a period ranging from 35 to 60 d. $Wt_{loss\text{-}sustained}$ subjects were those showing via medical records the successful maintenance of a reduced body weight for >1 y, without recent attempts to achieve further weight reduction. Those subjects were admitted to the CRC, and their caloric intake was adjusted until weight stability was achieved. Measurements were made starting at 0900–1000 while subjects were in a postabsorptive state.

Body composition and energy expenditure

Body composition was measured by using hydrodensitometry (33). Total EE for 24 h (TEE) was assessed on the basis of precise titration of fed calories of a liquid formula diet necessary to maintain body weight with a variance of <10 g/d over ≥14 d (3). The constancy of body composition, as well as weight stability, was confirmed by showing that the respiratory quotient (RQ) for subjects at rest in the postabsorptive state did not differ significantly from the formula quotient of the liquid formula diet—0.85 (3). Because weight and body composition were constant over the weeks before testing, the energy ingested as liquid formula must equal the TEE. Ongoing net increases or decreases in fat mass while at stable total weight would be reflected in respective increases or decreases in the RQ relative to the formula quotient (3). Our group previously showed that TEE measured by such caloric titration is highly correlated with TEE directly measured by the doubly labeled water method ($R^2 = 0.88$) (6).

Resting energy expenditure (REE) was measured by indirect (hood) calorimetry sampling every 30 s for a period of ≥30 min at 0900 while subjects were in bed and in a postabsorptive state (6). Subjects underwent multiple measures of REE throughout the study so that they were well accommodated to the procedure during testing periods. The RQ for each subject remained between 0.83 and 0.86 during all tests that were performed during the weight-stability period, designated as such on the basis of the lack of day-to-day variation in body weight ($P < 0.0001$). The stability of the RQ at values predicted by the formula quotient, coupled with the low within-subject variation in REE measured independently and as part of the determination of the thermic effect of food (TEF), indicates the reproducibility of this measure.

TEF was calculated as calories expended above REE after ingestion of liquid formula calories equivalent to 60% of REE measured on the day of testing as described below. Briefly, following the measurement of REE on the day that TEF was measured, subjects ingested dietary formula with a caloric content equal to 60% of the measured REE. Oxygen consumption and carbon dioxide production were measured by hood calorimetry for 30 min at 2 and 4 h after the feeding. The area of the polygon whose base is the prefeeding measured REE, and whose other vertexes are REE measured at 0900, 1100, and 1300, quantifies the increase in EE during the 4 h after ingestion of food. The fraction of ingested calories accounted for by the area of this polygon was multiplied by the weight-maintaining 24-h caloric intake to estimate TEF (6).

NREE, defined as energy expended above resting and TEF in physical activity, was calculated by using the following equation:

$$NREE = TEE - (REE + TEF) \qquad (1)$$

Statistical analysis

Data were analyzed using STATISTICA software (version 6.0; Statsoft, Tulsa, OK) (34). Data are presented as means ± SEMs. EE data are presented both as absolute and residual kcal/d. Residual analyses were performed to determine whether there were significant effects of short- or long-term duration of weight loss on measures of EE after adjustment for age and body composition and to confirm whether the current population of $Wt_{initial}$ subjects did not differ significantly from other subjects similarly studied in the present protocol (35). Multiple linear regression equations were generated relating measures of EE to sex, age, fat-free mass (FFM), and fat mass (FM) in the remaining 83 subjects who have completed studies at $Wt_{initial}$; this group did not include any of the subjects in the trios reported in the present study. Characteristics of these 83 subjects and data from regression equations are presented in **Table 2**.

Partial correlations for sex effect were not significant in these analyses, nor was there any improvement in the overall fraction of the variance in any measure of EE accounted for by the inclusion of sex. Therefore, in our final analyses, only regression equations relating TEE, REE, and NREE to age, FFM, and FM were used (Table 2). Residuals were calculated for each subject as the difference between actual measured or calculated values of EE for the subjects in this study and those values predicted on the basis of the regression equations relating EE to age, FFM, and FM in the 83 other subjects similarly studied at $Wt_{initial}$. Between-group comparisons were made by analysis of variance. Significance was prospectively defined as $P < 0.05$.

RESULTS

Subjects

By virtue of the selection process, there were, as anticipated, no significant differences in body weight or composition among the 3 types of subjects (Table 1). As expected, within-trio phenotypic variance increased as body weight increased. Moreover—also as expected, because subjects were matched by weight rather than body composition—within-trio variance of FM and FFM mass was greater than that of body weight.

Energy expenditure

Absolute values of TEE and NREE were significantly greater in the $Wt_{initial}$ group than in the $Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$ groups. Mean residual differences between actual values of TEE, REE, and NREE and those values predicted on the basis of regression equations relating EE to age and body composition in 83 other subjects studied at $Wt_{initial}$ were significantly less than zero in the $Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$ groups. In addition, residuals for TEE and NREE were significantly lower in the

TABLE 2
Residual analyses in 83 subjects studied at their usual weight (maintained for ≥6 mo)[1]

Regression equations	Age	Fat-free mass	Fat mass	Intercept	Overall *R*	*P*
TEE						
B	−9.1	30.8	10.1	891	0.91	<0.001
Partial *R*	−0.21	0.75	0.61			
P	0.056	<0.001	<0.001			
REE						
B	−0.3	18.7	5.6	416	0.83	<0.001
Partial *R*	−0.008	0.61	0.44			
P	0.94	<0.001	<0.001			
NREE						
B	−9.3	10.2	5.1	471	0.69	<0.001
Partial *R*	−0.25	0.40	0.40			
P	0.027	<0.001	<0.001			

[1] n = 42 M, 41 F. TEE, total energy expenditure in 24 h; REE, resting energy expenditure; NREE, nonresting energy expenditure. The $\bar{x} \pm$ SEM (range in parentheses) subject characteristic values in these 83 subjects were 28.9 ± 0.9 (19–45) y, 60.1 ± 1.6 (34.5–110.8) kg, 42.1 ± 3.3 (5.2–112.2) kg, 2906 ±81 (1500–5000), 1777 ±53 (1040–3358), and 1031 ±45 (159–2420) for age, fat-free mass, fat mass, TEE, REE, and NREE, respectively. The regression equations relating 24-h TEE, REE, and NREE to age, fat-free mass, and fat mass were used to calculate residual data presented in Table 3. "B" refers to the coefficient for each variable in the overall regression equation relating energy expenditure to body composition and age. Partial correlations and *P* values are given to indicate the independent contribution of each independent variable to the overall regression equation. Inclusion of sex did not improve any of the correlations and was not significantly correlated with any of the measures of energy expenditure; therefore, sex was not included as an independent variable.

$Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$ groups than in the $Wt_{initial}$ group. No significant differences in these variables were noted between the $Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$ groups (**Table 3** and **Figure 1**), which confirms the prolonged persistence of metabolic phenotypes in weight-reduced subjects.

DISCUSSION

The negative energy balance required for the dynamic loss of body energy stores (mainly FM) is accompanied by reductions in EE per unit of metabolic mass that are reversed by refeeding (9, 16, 36). The question of whether this disproportionate decline in EE persists after dynamic weight loss has ended, but while body weight is being maintained below initial body weight, is critical to an understanding of the biological basis for the very high recidivism to obesity seen in otherwise successfully treated patients (28, 29). We previously reported persistent reductions in EE—corrected for metabolic mass and age—in subjects maintaining a reduced body weight for periods of ≈3 mo after cessation of weight loss (3–6, 37). These reductions in EE could reflect transient carryover of the metabolic consequences of negative energy balance or could be a reflection of physiologic responses to reduced body fat per se (or both). The distinction between these 2 possibilities is critical to an understanding of weight homeostasis in human subjects.

The major finding of the present study is that there are similar, significant declines in TEE, NREE, and, to a lesser extent, REE in subjects maintaining a reduced body weight, regardless of whether that reduced weight has been maintained for weeks or years. In other words, bioenergetic responses to maintenance of a reduced body weight do not wane with time.

Studies in this laboratory and elsewhere have previously reported significantly reduced energy requirements in obese women who had maintained a reduced weight for periods of 4 to 6 y (1) and in subjects who were stable at their reduced weight months after substantial weight loss (38). Other studies did not detect significant changes in EE corrected for changes in metabolic mass in weight-reduced subjects (23–27). Some of those investigators concluded that the high recidivism rate after weight loss is predominantly due to patients' difficulties in adhering to a prescribed diet that may not differ substantially from the diet required to maintain the same weight and activity level in a person at his or her usual body weight (30). On the basis of the current study, it appears incorrect to dismiss persistent physiologic declines in EE after weight loss as being minimally contributory or not contributory to the difficulty of sustaining weight loss. Elsewhere, our group has presented data indicating *1*) that the changes in systems regulating both the energy intake and energy output that occur during reduced-weight maintenance act coordinately to favor the regain of lost weight and 2) that many of these changes are reversed by the restoration of circulating leptin concentrations to pre-weight-loss levels and are therefore the consequences of persistent relative hypoleptinemia long after weight loss has ended (4, 39–41). The long-term persistence of weight-reduced phenotypes after weight loss suggests that leptin signaling is important not only in systems affecting both energy intake and output but also in both short-term and long-term regulation of body energy stores.

What may account for the discrepancies among studies? The achievement of weight stability is difficult with a mixed-meal diet because day-to-day variations in dietary salt or carbohydrate content may affect water weight without necessarily affecting metabolic mass. The bias in out-patient weight-maintenance studies is clearly against the detection of persistent declines in energy metabolism because of the likelihood that subjects are in a state of positive energy balance (42). That is, because of the high rate of recidivism to previous levels of adiposity, weight-reduced persons are more likely to be gaining weight, even if slowly (28, 29).

A decline in energy expended in low-level physical activity accounts for most of the decrease in TEE in weight-stable subjects after weight loss (3–6). In weight-reduced humans and rodents, weight loss of 5% to 20% is generally associated with an increase in time spent in physical activity; however, with greater degrees of weight loss, this pattern may be reversed (43). An

TABLE 3
Energy expenditure of the study subjects[1]

	24-h Total energy expenditure (TEE)		24-h Resting energy expenditure (REE)		24-h Nonresting energy expenditure (NREE)		24-h Thermic effect of feeding (TEF)
Trios and groups	kcal/d	Residual kcal/d	kcal/d	Residual kcal/d	kcal/d	Residual kcal/d	kcal/d
Trio 1: women							
$Wt_{loss\text{-}sustained}$	1700	−447	1210	−171	422	−235	68
$Wt_{initial}$	2200	−69	1297	−48	793	−48	110
$Wt_{loss\text{-}recent}$	1950	−225	1196	−149	590	−154	164
Trio 2: women							
$Wt_{loss\text{-}sustained}$	2100	−63	1331	−32	620	−86	149
$Wt_{initial}$	2450	281	1510	152	854	134	86
$Wt_{loss\text{-}recent}$	1800	−484	1170	−203	512	−315	118
Trio 3: women							
$Wt_{loss\text{-}sustained}$	1950	−219	1356	−204	509	−265	85
$Wt_{initial}$	2100	−304	1212	−246	720	−140	168
$Wt_{loss\text{-}recent}$	2350	−344	1685	76	578	−398	87
Trio 4: men							
$Wt_{loss\text{-}sustained}$	2600	−200	1672	−91	742	−160	186
$Wt_{initial}$	2700	82	1612	−40	950	120	130
$Wt_{loss\text{-}recent}$	2350	−460	1607	−67	611	−399	132
Trio 5: men							
$Wt_{loss\text{-}sustained}$	2800	−679	19 144	66	708	−304	178
$Wt_{initial}$	3450	350	1850	−42	1386	322	214
$Wt_{loss\text{-}recent}$	2400	−436	1646	−115	684	−262	120
Trio 6: women							
$Wt_{loss\text{-}sustained}$	2750	−680	1675	−393	882	−383	193
$Wt_{initial}$	3600	211	2167	141	1295	19	138
$Wt_{loss\text{-}recent}$	2900	−639	1904	−254	841	−429	155
Trio 7: women							
$Wt_{loss\text{-}sustained}$	3200	−817	2195	−191	851	−653	153
$Wt_{initial}$	3600	−431	2210	−172	1300	−222	288
$Wt_{loss\text{-}recent}$	2750	−634	1678	−417	807	−385	265
Overall values							
$W_{loss\text{-}sustained}$	2443 ± 203[2]	−422 ± 104[3]	1622 ± 133	−143 ± 55[4]	677 ± 64	−298 ± 69[3]	130 ± 20
$Wt_{initial}$	2871 ± 251[5]	11 ± 110	1694 ± 150	−40 ± 54	1043 ± 105[6]	26 ± 69	162 ± 26
$Wt_{loss\text{-}recent}$	2357 ± 149	−460 ± 56[3]	1555 ± 103	−161 ± 58[4]	660 ± 47	−334 ± 67[3]	156 ± 21

[1] $Wt_{loss\text{-}sustained}$, subjects maintaining a weight loss of ≥10% over periods ranging from 1 to 6 y and reporting being weight-stable for ≥1 y; $Wt_{initial}$, subjects at their usual weight who have been weight-stable for ≥6 mo; $Wt_{loss\text{-}recent}$, subjects who have lost ≥10% of their weight on an in-patient basis and have maintained the reduced weight for ≥3 wk. Maintenance of a reduced body weight in $Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$ subjects is associated with lower absolute TEE and NREE. Residual values of TEE, REE, and NREE are all significantly less than zero at $Wt_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$. Residual values were calculated as the difference between observed values of energy expenditure and those predicted on the basis of regression equations relating energy expenditure to age, fat-free mass (FFM), and fat mass (FM) in 83 subjects studied at $Wt_{initial}$ but not included in any of the experimental trios. These regression equations are *1)* TEE = −9.1 (age) + 30.8 (FFM) + 10.1 (FM) + 891, where adjusted R^2 = 0.84 and $P < 0.001$; *2)* REE = −0.3 (age) + 18.7 (FFM) + 5.6 (FM) + 416, where adjusted R^2 = 0.69 and $P < 0.001$; and *3)* NREE = −9.3 (age) + 10.2 (FFM) + 5.1 (FM) + 471, where adjusted R^2 = 0.47 and $P < 0.001$. Semipartial correlations for each independent variable are shown in Table 2.

[2] $\bar{x}$ ± SEM (all such values).

[3] $P < 0.01$ compared with zero and compared with $Wt_{initial}$.

[4] $P < 0.05$ compared with zero.

[5] $P < 0.05$ compared with $W_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$.

[6] $P < 0.01$compared with $W_{loss\text{-}sustained}$ and $Wt_{loss\text{-}recent}$.

increase in spontaneous physical activity in weight-reduced subjects also would tend to mask any declines in EE (44). In studies of skeletal-muscle work efficiency in weight-reduced subjects using this experimental design (4, 37), our group found that the maintenance of a reduced weight is associated with an increase in skeletal-muscle work efficiency at low levels of physical activity but did not find any within-subject changes in the amount of time spent in physical activity in the CRC after weight loss.

Therefore, studies of EE in weight-reduced subjects confront the difficult, but necessary, task of either quantifying or controlling the quality and quantity of physical activity, in order to enable an accurate comparison of subjects with themselves or

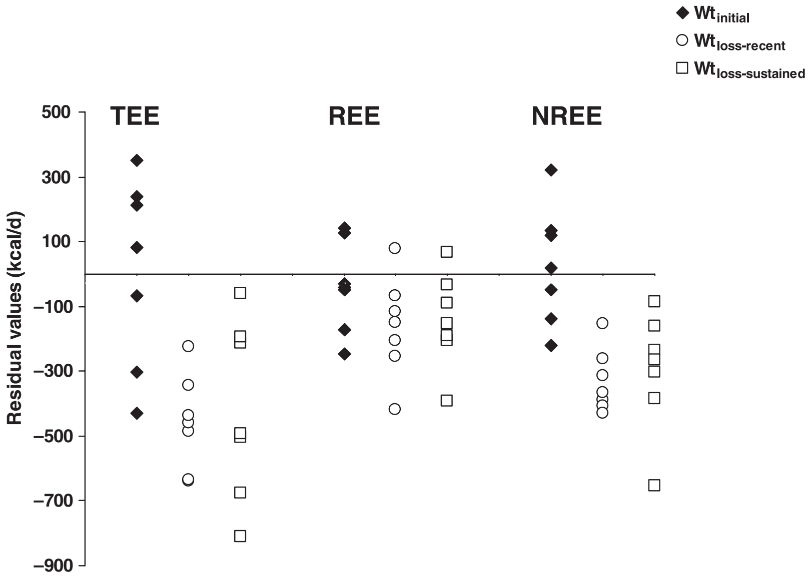

FIGURE 1. Residual values of energy expenditure measurements in subjects compared with predicted values based on regression equations relating energy expenditure to age, fat-free mass, and fat mass in a separate population of 83 subjects studied at usual body weight. TEE, total energy expenditure for 24 h; FFM, fat-free mass; FM, fat mass; REE, resting energy expenditure; NREE, nonresting energy expenditure. These regression equations are *1*) TEE = −9.1 (age) + 30.8 (FFM) + 10.1 (FM) + 891, where adjusted $R^2 = 0.84$ and $P < 0.001$; *2*) REE = −0.3 (age) + 18.7 (FFM) + 5.6 (FM) + 416, where adjusted $R^2 = 0.69$ and $P < 0.001$; and *3*) NREE = −9.3 (age) + 10.2 (FFM) + 5.1 (FM) + 471, where adjusted $R^2 = 0.47$ and $P < 0.001$. Horizontal lines denote arithmetic means for each group. TEE, REE, and NREE residuals are significantly less than zero at $Wt_{loss\text{-}recent}$ and $Wt_{loss\text{-}sustained}$. TEE and NREE residuals are significantly lower at $Wt_{loss\text{-}recent}$ and $Wt_{loss\text{-}sustained}$ than at $Wt_{initial}$.

others. By virtue of restrictions on activity in a confined space and the inability to mimic the activities of daily living by using stationery bicycles or other exercise equipment (6), chamber calorimetry is biased against detecting declines in energy expended in physical activity after weight loss. Out-patient studies have the advantage of being more representative of real-life circumstances, but they are confounded by the effects of weight reduction on the amount of time spent being physically active (44). This dilemma is illustrated in a study by Weinsier et al (27, 45), who reported that EE determined by differential isotopic excretion rates of ^2H_2O and $H_2{}^{18}O$ in women studied as outpatients did not differ significantly before and after weight reduction. However, these women reported spending an additional 30% of their time being physically active after weight loss (27, 45), which implied that they were more metabolically efficient and were actually expending fewer calories per unit of work (per unit of metabolic mass) after weight loss (45), as our group found by direct measurement of skeletal muscle work efficiency in weight-reduced subjects (4, 37).

We have endeavored to meticulously control for the factors that confound this type of study. First, these subjects were weight-stable to a degree of precision that could not be achieved in an out-patient setting or with a solid-food diet. Second, daily diet composition was constant for each subject and among subjects, which enabled a study over many weeks in subjects who were more closely matched by weight, diet, and physical activity than were those previously reported. Third, physical activity was limited by the restriction of subjects to the CRC, although, even with this limitation, between-subject differences in spontaneous physical activity are likely; these differences were not measured (35). Fourth, the present experimental protocol allowed sufficient physical activity [as compared with a chamber calorimeter (6)] to facilitate detection of the declines (≈30%) in NREE that occur during maintenance of a weight reduction.

The present study confirmed that a clinically significant decline in EE after weight loss occurs, that NREE is the primary compartment in which EE is reduced, and that these reductions in EE persist over an extended period of time—perhaps indefinitely. Clinically, the present results are consistent with those of earlier studies, and they indicate that high levels of physical activity are characteristic of persons who maintain a reduced weight over prolonged periods (29, 46–50).

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